Positron emission tomographic scanning in the diagnosis and staging of non–small cell lung cancer 2 cm in size or less

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Objective: Several studies have suggested that positron emission tomography is more accurate than computed tomography for the staging of non–small cell lung cancer and can reduce the rate of unnecessary thoracotomy in patients with potentially resectable disease. However, there are few data on the utility of positron emission tomography in the diagnosis of patients with tumors of 2 cm or less in size.

Methods: Patients with cT1/cT2 tumors of 2 cm or less in size were retrospectively reviewed. All had a computed tomographic scan, as well as a positron emission tomographic scan on a dedicated scanner, with a standard uptake value reported. A standard uptake value of 2.5 g/mL or greater was considered positive. The results of computed tomography and positron emission tomography were correlated with pathologic results after either resection (n = 60) or mediastinoscopy (n = 4).

Results: Sixty-four patients (38 women; mean age, 66 years) had a mean tumor size of 1.4 cm (range, 0.7-2.0 cm). Forty-three patients had adenocarcinoma, 13 had adenocarcinoma–bronchioloalveolar carcinoma, 5 had squamous cell carcinoma, and 3 had other tumor types. Twenty-nine (45%) tumors had negative positron emission tomographic results. Both tumor size (>1 cm vs ≤1 cm) and cell type (adenocarcinoma−bronchioloalveolar carcinoma vs all other cell types) were significant predictors of positron emission tomography uptake in the primary tumor ($P = .05$ and .01, respectively). Nodal metastases were detected pathologically in 11 (17%) patients (5 N1 and 6 N2). Positron emission tomographic sensitivity and specificity for nodal metastases were only 45% and 89%, respectively. There was no statistically demonstrable survival difference between positron emission tomography–positive and positron emission tomography–negative tumors (3-year survival of 87% vs 100%, respectively).

Conclusion: Positron emission tomographic scanning has no demonstrable benefit in the diagnosis, staging, or prognosis of patients with tumors of 2 cm or less in size.

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Positron emission tomographic (PET) scanning has been shown to be accurate in the diagnosis and staging of non–small cell lung cancer (NSCLC).[1-6] PET scanning is superior to conventional computed tomographic (CT) scanning in staging mediastinal lymph nodes, with a reported average sensitivity and specificity for PET of 80% and 90%, respectively.[7] In addition, PET scanning has demonstrated accuracy in determining the extent of extrathoracic disease, such as bone, adrenal, and hepatic metastases.[8-10] Recently, both the American College of Surgeons Trial (ACOSOG Z0050) trial and the PET in Lung Cancer Staging trial determined that PET appeared to reduce the incidence of unwarranted thoracotomies.[11,12] Based in large part on these studies, PET scanning has become a routine component of the preoperative evaluation of patients with NSCLC.

Abbreviations and Acronyms
BAC = bronchioloalveolar carcinoma
CT = computed tomography
FDG = fluorodeoxyglucose
NSCLC = non–small cell lung cancer
PET = positron emission tomography
SUV = standard uptake value

Over the past decade, the increased use of CT scanning has resulted in a relative decrease in the median tumor size of resected NSCLC,[13] yet little is known in regard to the utility of PET in the diagnosis and staging of such small lesions. None of the aforementioned trials focused on patients with tumors of 2 cm or less in size. We performed a retrospective analysis to determine the role of PET in T1 or T2 NSCLC of 2 cm or less in size.

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Patients and Methods

Patient Population

We conducted a retrospective review of all patients with primary tumors of 2 cm or less in size from our thoracic surgery cancer database at the Weill Medical College of Cornell University. We included patients with NSCLC of 2 cm or less in size who had a mediastinoscopy alone or a lobectomy with a mediastinal node dissection between 2001 and 2004. All had a single tumor of 2 cm or less determined by means of CT measurement, no history of cancer in the previous 5 years, and a PET scan performed on a dedicated scanner, with a standard uptake value (SUV) reported. We excluded patients who had prior neoadjuvant chemotherapy, those presenting with ground-glass opacities, or those found to have bronchioloalveolar carcinoma (BAC) or well-differentiated neuroendocrine carcinoma on final histology.

Staging

All patients were evaluated preoperatively on the basis of a complete history and physical examination, a CT scan of the chest and upper abdomen, and a PET scan. Brain scanning was obtained if clinically indicated. A clinical TNM stage was then determined.

All CT scan reports, actual films, or both were reviewed, and exact tumor size and nodal status were determined. Tumors were classified as central or peripheral when possible. We defined a peripheral tumor as one lying in the outer one third of the lung parenchyma. Enlarged mediastinal lymph nodes were defined as lymph nodes greater than 1 cm in the short axis. PET scans were obtained at facilities with a dedicated PET scanner, and only those reports that provided an actual maximum SUV were used for this study. We defined a maximum SUV of 2.5 g/mL or higher as a positive reading.[14] Pathologic staging was obtained either after resection with mediastinal lymph node dissection or after mediastinoscopy.

Statistical Analysis

The associations between PET uptake and tumor size (>1 cm vs ≤ 1 cm) and between PET uptake and cell type (other vs BAC) were explored by using the Pearson χ^2 test. Patient survival was analyzed with Kaplan-Meier product-limit estimation. The independent effect of tumor size as a continuous variable on PET uptake was examined by using Pearson correlation and a multivariable linear regression analysis. All P values were 2 sided, with statistical significance evaluated at the .05 α level. All analyses were performed with SPSS version 11.0.3 software (SPSS Inc, Chicago, Ill). This study was approved by the Institutional Review Board of the Weill Medical College of Cornell University.

TABLE 1. Demographics and clinicopathologic characteristics

		n	%
Age (y)	Mean 65.94 (46-81)		
Sex			
	F	38	59.4
	M	26	40.6
Smoking status			
	Smoker	56	87.5
	Nonsmoker	6	9.4
	Unknown	2	3.1
Tumor location			
	Central	6	9.0
	Peripheral	44	68.0
	NA	14	22.0
Tumor size (cm)			
Mean	1.395		
Range	0.7-2.0		
<1 cm		9	14.9
1-2.0 cm		55	85.9
Histology			
	Adenocarcinoma	43	67.2
	Adenocarcinoma-BAC	13	20.3
	Squamous carcinoma	5	7.8
	NSCLC NOS	1	1.6
	Large cell	1	1.6
	Poorly differentiated	1	1.6
T1:T2		*52:7	

NA, Not available; *BAC,* bronchioloalveolar carcinoma; *NSCLC,* non–small cell lung cancer; *NOS,* not otherwise specified. *One patient with T4 disease and 4 patients with mediastinoscopy only.

Results

Patient Population

During the study period, 222 patients underwent either resection or mediastinoscopy for tumors of 2 cm or less in size. One hundred forty of these patients had a preoperative PET scan, of whom 83 had dedicated PET scans with SUV data. Fourteen patients with ground-glass opacities and 5 with multiple nodules were excluded. Therefore the final study population consisted of 64 patients, 60 after primary resection and 4 after a positive mediastinoscopy alone. Patient demographics and tumor characteristics are depicted in Table 1. Sixty-four patients (38 women; mean age, 66 years) had a mean tumor size of 1.4 cm (0.7-2.0 cm).

TABLE 2. PET results

PET		
Positive	n = 35	54.7%
Negative	n = 29	45.3%
Maximum SUV (mean)	4.04	
Maximum SUV (range)	0.9-16.0	
PET (+) by size		
<1 cm	4/9	44.4%
1-2.0 cm	31/55	56.4%
PET (+) by cell type		
Adenocarcinoma	25/43	58%
Adenocarcinoma/BAC	3/13	23%
Squamous carcinoma	5/5	100%
Other	2/3	66%

PET, Positron emission tomography; SUV, standard uptake value; *BAC*, bronchioloalveolar carcinoma.

Forty-three patients had adenocarcinoma, thirteen had adenocarcinoma with BAC features, 5 had squamous cell carcinoma, and 3 had other tumor types.

Thirty-five tumors were PET positive (55%), whereas 29 (45%) were not fluorodeoxyglucose (FDG) avid (Table 2). Both tumor size (>1 cm vs ≤1 cm: 61% vs 31%, $P = .05$) and cell type (adenocarcinoma-BAC vs all other cell types: 63% vs 23%, $P = .01$) were found to be significant predictors of positive PET uptake (SUV ≥ 2.5) by means of the Pearson χ^2 test. The analysis was repeated for both tumor size and cell type with an SUV cutoff of 2.0 g/mL, and the results were essentially unchanged (data not shown). When analyzed as continuous variables by using Pearson correlation, tumor size and SUV showed a significant association ($\rho = 0.3$, $P \leq .05$). When tumor size was analyzed by means of multivariable linear regression with age, sex, histology, and pathologic stage as covariables, it was a significant independent predictor of SUV ($b = 2.7$, $P = .02$; Table 3).

Nodal metastases were detected pathologically in 11 (17%) patients (5 N1 and 6 N2). PET sensitivity and specificity for nodal metastases was 45% and 89%, respectively (Table 4). Of the 6 patients with a false-negative PET scan for nodal disease, 4 had a positive PET scan and 2 had a false-negative scan in the primary tumor. Also, only one patient with a false-negative PET scan in the mediastinum had an adenocarcinoma with a BAC component.

TABLE 3. Multivariable regression analysis

Factor	*b*	*t*	*P* value
Constant	2.97	0.93	.36
Age	−0.044	−1.01	.32
Sex	0.96	1.10	.28
Histology (other, BAC)	−1.47	−1.25	.22
Pathologic stage(IA, non-IA)	−0.035	−0.04	.97
Pathologic tumor size	2.67	2.42	.02

BAC, Bronchioloalveolar carcinoma.

TABLE 4. Comparison of PET and pathologic N (pN) stages (n = 64)

	pN0	pN1	pN2	Total
PET N0	47	4	2	53
PET N1	2	0	2	4
PET N2	4	1	2	7

PET, Positron emission tomography.

Although the study was not intended to evaluate the accuracy of CT scanning for nodal staging, the overall sensitivity and specificity for N1 and N2 disease combined was 36% and 100%, respectively (Table 5). There was no statistically demonstrable survival difference between PET-positive and PET-negative tumors (3-year survival of 87% vs 100%, respectively; Figure 1). However, there are too few patients in this study to detect a small but potentially real difference in survival between these 2 groups.

Discussion

PET is a relatively new technology that holds the promise of improved accuracy in the diagnosis and staging of patients with NSCLC.[7,15] As a result of numerous reports proclaiming the benefit of PET, it has become widely adopted as the standard of care for the evaluation of patients with NSCLC, regardless of clinical stage. However, the role of PET scanning in the diagnosis and staging of small (≤2 cm) NSCLC has not been thoroughly examined.

In the current report, which is primarily composed of peripherally located small adenocarcinomas (68%), only 55% of these tumors were FDG avid, despite the exclusion of patients with pure BAC, lesions known not to accumulate FDG.

These data are applicable to tumors larger and smaller than 1.0 cm in size and have obvious implications for the use of PET as the definitive diagnostic procedure for peripheral pulmonary nodules that otherwise appear clinically suspicious. Multiple studies have shown an improved efficacy with PET compared with conventional CT for the evaluation of mediastinal lymph nodes.[7,11,14] PET sensitivity and specificity are consistently reported in the 80% range, yet in this analysis PET sensitivity for the detection of N1 or N2 disease was 45%, with a specificity of 89%.

TABLE 5. Comparison of CT and pathologic N (pN) stages (n = 64)

	pN0	pN1	pN2	Total
CT N0	53	4	3	60
CT N2	0	1	3	4

CT, Computed tomography.

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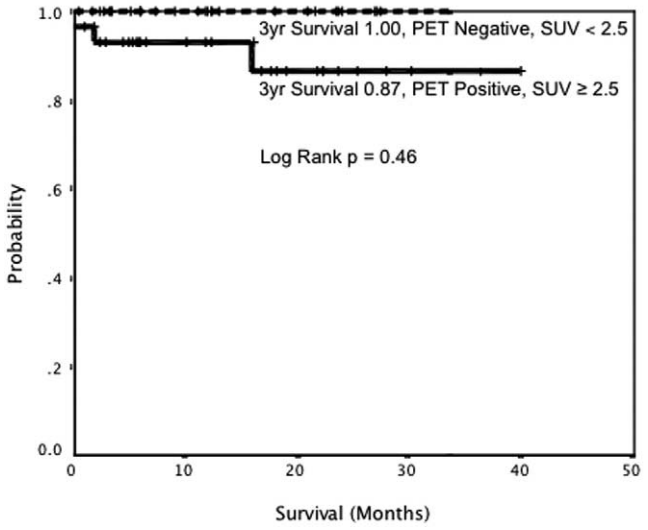

Figure 1. Survival for positron emission tomography *(PET)*–positive and PET-negative tumors. *SUV*, Standard uptake value.

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The lack of sensitivity cannot be explained solely by the lack of uptake in the primary lesion because in only 2 of 6 cases of false-negative PET scans in the mediastinum were the primary lesions inactive. Others have recently shown that small microscopic nodal deposits will not be FDG avid.[16] In this report, although nodal deposits were not measured, most of the node-positive patients had single-level microscopic disease, which might explain the lack of nodal sensitivity. Although the PET sensitivity in the mediastinum appears to be less than in previous reports, it is comparable with the 61% sensitivity reported in the Z50 trial.[11] Similarly, in another randomized trial of PET in patients with stage I and II NSCLC, PET sensitivity for detecting single-station nodal disease was 55%.[17]

Numerous PET studies have now been performed that have used a reduction in unwarranted thoracotomies as their end point.[11,17] In our analysis there were no patients with occult metastatic disease or nodal IIIB disease. Overall, PET did not lead to a reduction in unwarranted thoracotomies. However, given the retrospective nature of this study, a prereferral bias cannot be excluded. Additionally, the 64 patients in this study were selected from 222 potential candidates on the basis of a rigid set of selection criteria.

There are a number of limitations in this study. A number of different nuclear and CT scanning facilities were used in the evaluation of our patient population. However, studies that did not fall within our quality criteria were excluded, and all decisions in regard to further evaluation and treatment were made by 2 surgeons. We therefore believe that these data reflect the current practices of thoracic oncologists.

The role of PET scanning in the detection of occult metastatic disease is not addressed by our work. This study, as previously noted, contains a highly select group of patients subject to inherent referral and selection biases. However, given the low reported incidence (0.5%-5%) of silent metastases in this group of patients, it would seem unlikely that PET would confer much advantage.[18-21]

In summary, although PET has been liberally applied for the evaluation of many patients with lung cancer, it does not appear to offer a clear advantage in patients with small, peripherally located T1 or T2 tumors of less than 2 cm in size. Furthermore, the use of PET in the evaluation of clinically suspicious small, solitary pulmonary nodules appears to carry a high false-negative rate and should not be the only basis for clinical management.

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